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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,449	09/19/2006	Per Rydberg	1515-1093-1	8951

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EXAMINER
MUI, CHRISTINE T

ART UNIT	PAPER NUMBER
1797	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,449	RYDBERG, PER	
	Examiner	Art Unit	
	CHRISTINE T. MUI	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,10,16-19,21,23-25,27-37,41-45,47 and 49-61* is/are pending in the application.

4a) Of the above claim(s) *45,47 and 50-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,10,16,17,19,21,23-25,33-37,41,44,49 and 56-60* is/are rejected.

7)☒ Claim(s) *18,27-32,42,43 and 61* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *19 September 2006; 04 May 2007; 27 December 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 45, 47 and 50-52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected product, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 07 May 2009.

2. Applicant has amended the claims filed on 07 May 2009, where the claims drawn to Group I and Group II where the limitation are consistent and are have a common special technical feature. The requirement for restriction is improper in part and the restriction only between Groups I and II are withdrawn.

3. Applicant's election with traverse of Group I in the reply filed on 07 May 2009 is acknowledged. The traversal is on the ground(s) that the Groups I to V do not constitute a burden to the examiner. This is not found persuasive because Group III is just drawn to a compound that exists and is well know as a compound by itself. Group IV is drawn to a container used for performing the method; containers are old and well known in the art used for analyzing fluids; such as cuvettes, vessels, crucibles, beakers. Groups V and VI are drawn to an apparatus for performing the method and a computer program, respectively that are known as disclosed by Rydberg.

The requirement is still deemed proper and is therefore made FINAL.

The current pending claims in the instant application are claims 1-6, 10, 16-19, 21, 23-25, 27-37, 41-44, 49 and 53-61.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 53 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 53 recites the limitation "size-discriminating ultrafiltration" in line 2 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

7. Claim 54 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 54 recites the limitation "ultracentrifugation" in line 2 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

9. Claim 55 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 55 is dependent on cancelled claim. Examiner is unsure as to which claim it is supposed to depend on.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. Claims 1-6, 16, 19, 21, 23, 25, 33-37, 44, 49, 56-58, 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kautiainen et al (herein referred 'Kautiainen'), and further in view of Rydberg et al, *Adducts to N-terminal valines in hemoglobin from butadiene metabolites* (herein referred 'Rydberg').

14. Regarding claims 1-5, 16, 19, 21, 23, 25, 33-36, 44, 56-58, 60, the reference Kautiainen discloses a method based on the analysis by liquid chromatography/electrospray ionization mass spectrometry of the N-modified N-terminal peptides enriched after trypsin digestion of globin. In the Kautiainen study, Hb samples from mice were injected with DEB, dissolved in saline and the blood of the animals was collected in heparinized tubes for Hb-adduct measurement and examined for the ring-closed adduct. The N-terminal pyrrolidine-heptapeptide was identified. To an aqueous solution of hepta-or ($^2H_8$) octapeptide, 40 μL of 0.26 DEB were added and incubated any remaining DEB was destroyed by the addition of TFA and the reaction product was analyzed by ESI-MS. This alkylated heptapeptide was used as a standard for the

determination of the retention time in HPLC. In the sample analysis, the globin from DEB treated mice was dissolved in 0.2 M ammonium hydrogen carbonate (pH 8.5). The internal standard and few μL of 10% sodium dodecyl sulphate were added to the samples digested with trypsin at a substrate to enzyme ratio of 20:1 for 16 h at 37°C. Quantification of adduct levels in the sample were carried out by LC/MS/MS, were based on abundance ratios of product ions of pyrrolidinium ions of N-terminal heptapeptide in the α-chain and of the internal standard (see abstract, pages 1848-1850).

15. Kautiainen does not disclose the fluid or solid in direct contact with an isothiocyanate reagent then separation by LC and detection by MS, but rather discloses the fluid or solid of digested globin was concentrated by the addition of trifluoroacetic acid to eliminate any DEP remaining in the sample (see page 1850). Kautiainen does disclose that it is known in another study that Rydberg mentions, is where N-terminal valines are detached from globin by pentafluorophenylthiohydantoins by a modified Edman degradation in reaction with pentafluorophenyl isothiocyanate, but analysis is done by GC/MS and the adducts to N-terminal valine in hemoglobin are determined (see page 1848, Rydberg: abstract, pages 196-197).

16. It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify Kautiainen by reacting the fluid or solid with an isothiocyanate reagent in order to successfully detach the N-terminal from the hemoglobin chain creating a molecule for analysis that does not create any side reactions or formation of unwanted chains or rings in the structure of the analyte.

17. Regarding claims 6 and 37, the references Kautiainen and Rydberg disclose the claimed invention except for where the adduct is a serum albumin adduct. It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the adduct as this is a matter of design choice of the experiment, where it is old and well know that serum adducts contain N-terminal amino acids.

18. Regarding claim 49, the references Kautiainen and Rydberg disclose the claimed invention except for specifically disclosing a kit containing all of the elements to perform the method of analyzing N-terminal adducts. However, it would have been obvious to one having ordinary skill in the art at the time the invention was made to incorporate all of the needed/required reagents and instrumentation required for analyzing the N-terminal adducts in accordance with the methods taught by Kautiainen and Rydberg in a kit form so as to make the method more convenient and easy to perform by having all of the necessary components in one centralized location facilitating quick and efficient analysis of steroid hormones without having to take extra time to assemble the various reagents and instrumentation required.

19. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kautiainen, in view of Rydberg as applied to claim 1 above, and further in view of Toriba et al (herein referred 'Toriba').

20. Regarding claim 10, the references Kautiainen and Rydberg disclose the claimed invention except for the reagent being specifically FITC. Toriba discloses that is well known in the art to use FITC, fluorescein isothiocyanate, to derivatize N-terminal amino acids. Toriba discloses that in the Edman sequence using this reagent, amino acids are

identified with HPLC (see page 732). It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the reagent being specifically FITC in order to enhance the detection sensitivity of amino acids.

21. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kautiainen, in view of Rydberg as applied to claim 16 above, and further in view of Toriba.

22. Regarding claim 17, the references Kautiainen and Rydberg disclose the claimed invention except for the enrichment step specifically consisting of ultracentrifugation. Toriba discloses the sample obtained is mixed with the reagent MTBD-NCS, 7-Methylthio-4-(2,1,3-benoxadiazolyl) isothiocyanate, the mixture is vortexed-mixed and heated at 50°C. The dipeptide and the reagent are now coupled and was then washed and subjected to HPLC for analysis (see page 734). It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the enrichment step in order to separate and isolate the analyte to create the most purified analyte for detection.

23. Claims 24 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kautiainen, in view of Rydberg as applied to claim 23 above, and further in view of Toriba.

24. Regarding claims 24 and 59, the references Kautiainen and Rydberg disclose the claimed invention except for the enrichment step specifically consists of centrifugation, washing and lysing and then heating. Toriba discloses the sample obtained is mixed with the reagent MTBD-NCS, 7-Methylthio-4-(2,1,3-benoxadiazolyl) isothiocyanate, the

mixture is vortexed-mixed and heated at 50°C. The dipeptide and the reagent are now coupled and was then washed and subjected to HPLC for analysis (see page 734). It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the enrichment step in order to separate and isolate the analyte to create the most purified analyte for detection.

25. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kautiainen, in view of Rydberg as applied to claim 33 above, and further in view of Toriba et al.

26. Regarding claim 41, the references Kautiainen and Rydberg disclose the claimed invention except for the reagent being specifically FITC. Toriba discloses that is well known in the art to use FITC, fluorescein isothiocyanate, to derivatize N-terminal amino acids. Toriba discloses that in the Edman sequence using this reagent, amino acids are identified with HPLC (see page 732). It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the reagent being specifically FITC in order to enhance the detection sensitivity of amino acids.

Allowable Subject Matter

27. Claims 18, 27-32, 42-43 and 61 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

28. Regarding claims 18 and 42, in the method for analyzing N-terminal adducts where the analyte is described in the instant claim especially where X is a

pentafluorophenyl group is not found in the prior art. In the references used, in the rejection above, the analyte determined is of Formula I and does not suggest any other molecule, since the references are based on the Edman method.

29. Regarding claim 27, the step of separation by size-discriminating ultra filtration in a size-discriminating ultra filtration tube and where the analyte is being bound to an ion exchange resin is not property taught nor suggested in prior art of record. The references used, disclose using chromatography then MS in their analysis steps. There is no suggestion to provide an additional step of separation.

30. Since claims 28-32 and 61 depend on claim 27 that is objected, these claims are also objected to as being dependent on a rejected base claim.

31. Regarding claim 43, in the specific method for analyzing an adduct in N-adducted amino acids or adducted N-terminal peptide or protein wherein the analyte being detected is of one listed in the instant claim according the method steps recited in claim 33 is not found in the prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTINE T. MUI whose telephone number is (571)270-3243. The examiner can normally be reached on Monday-Thursday 7-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Walter Griffin can be reached on (571) 272-1447. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CTM

/Walter D. Griffin/
Supervisory Patent Examiner, Art Unit 1797